

A General Methodology for the Enantioselective Synthesis of 1-Substituted Tetrahydroisoquinoline Alkaloids

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Dedicated to Prof. Dr. Antonio García Martínez on the occasion of his retirement

Keywords: Alkaloids / Heterocycles / Lactams / Asymmetric synthesis / Total synthesis

Starting from tricyclic lactam **2**, which is easily accessible by cyclocondensation of δ -oxoester **1** with (*R*)-phenylglycinol, a three-step synthetic route to enantiopure 1-substituted tetrahydroisoquinolines, including 1-alkyl-, 1-aryl-, and 1-benzyl-

tetrahydroisoquinoline alkaloids, as well as the tricyclic alkaloid (–)-crispine A, has been developed. The key step is a stereoselective α -amidoalkylation reaction using the appropriate Grignard reagent.

Introduction

The tetrahydroisoquinoline ring system is present in numerous structurally diverse natural products exhibiting a wide range of biological and pharmacological activities.^[1] In particular, simple 1-substituted tetrahydroisoquinolines are of great interest not only as alkaloids themselves but

also as useful key intermediates in the synthesis of more complex alkaloids. This has stimulated the development of a number of methodologies aimed at the enantioselective synthesis of 1-substituted tetrahydroisoquinoline derivatives^[2] (Figure 1).

In previous work, we demonstrated that phenylglycinol-derived oxazolopiperidone lactams are versatile scaffolds that allow the regio- and stereocontrolled introduction of substituents at different positions of the piperidine ring,

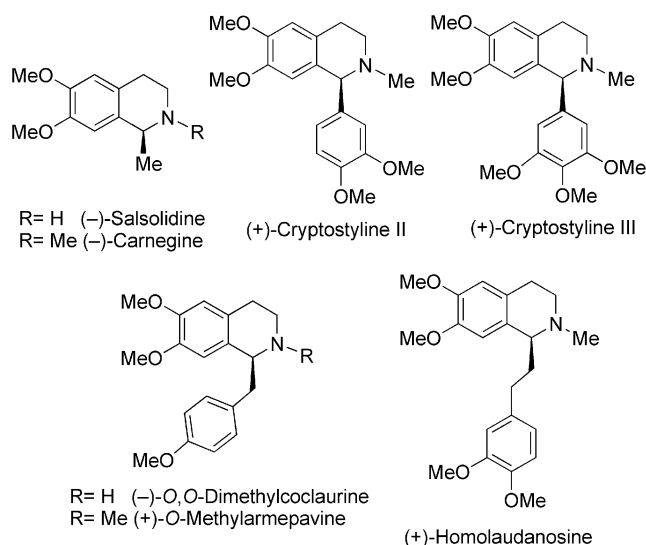
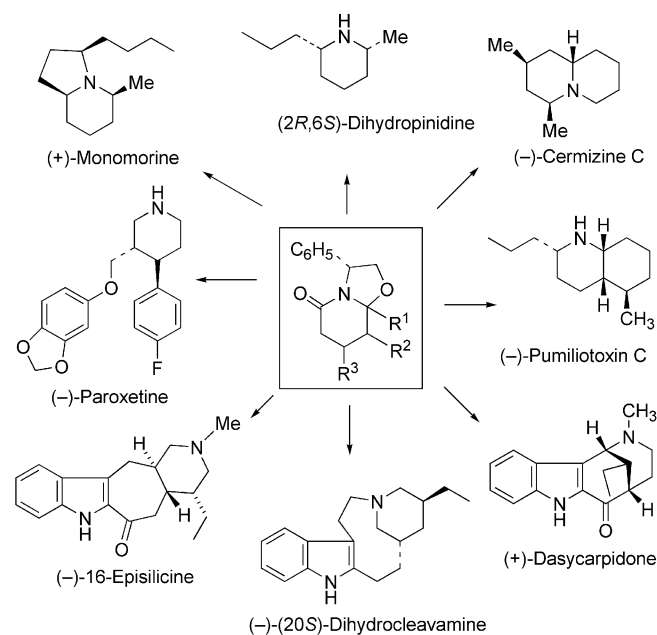


Figure 1. Selected 1-substituted tetrahydroisoquinoline alkaloids.

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Scheme 1. Natural and bioactive products prepared from phenylglycinol-derived lactams.

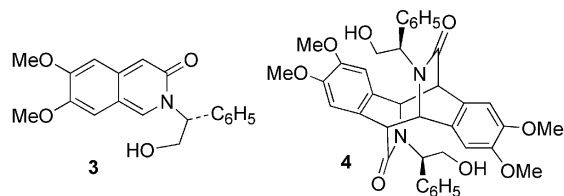
thus providing access to enantiopure substituted piperidines bearing virtually any type of substitution pattern, as well as to quinolizidine, indolizidine, decahydroquinoline, and complex piperidine-containing indole alkaloids^[3] (Scheme 1).

Results and Discussion

To further expand the synthetic potential of phenylglycinol-derived oxazolopiperidone lactams, we report here a general methodology for the enantioselective synthesis of 1-substituted tetrahydroisoquinoline alkaloids. The application of our enantiomeric scaffolding strategy^[4] would simply require starting from an appropriate benzo-fused oxazolopiperidone lactam and the subsequent stereocontrolled introduction of the substituent at the 1-position of the tetrahydroisoquinoline ring by an asymmetric α -amidoalkylation reaction.^[5]

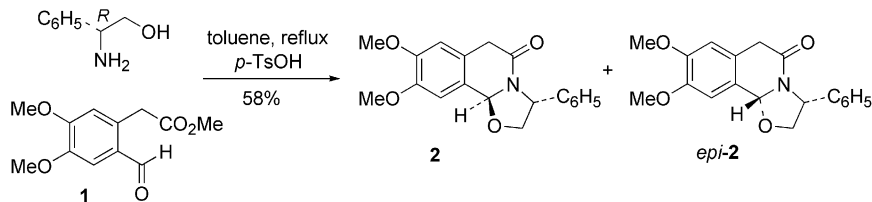
Tricyclic lactam **2** was envisaged as the pivotal intermediate of our synthesis. It was prepared in 52% yield by cyclocondensation of aldehyde ester **1**^[6] with (*R*)-phenylglycinol in refluxing toluene in the presence of a catalytic amount of *p*-TsOH (Scheme 2). The absolute configuration of lactam **2** was unambiguously determined by X-ray crystallographic analysis.^[7] Minor amounts (6%) of lactam *epi-2*, epimeric at the 2-position of the oxazolidine ring, were also formed.

In contrast with related *cis*-oxazolopiperidone lactams,^[8] minor *cis* lactam *epi-2* did not undergo epimerization under acidic conditions (1.2 N HCl, MeOH, r.t); isoquinolone **3** and trace amounts of dimer **4** were formed instead. This dimer was formed in 49% yield after prolonged acidic treatment (1.2 N HCl, MeOH, reflux, 66 h) of isoquinolone **3**.



Initial attempts to carry out the α -amidoalkylation reaction with a higher order cyanocuprate $[\text{Me}_2\text{Cu}(\text{CN})\text{Li}_2]$ in the presence of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ ^[9] resulted in failure, leading exclusively to isoquinolone **3**. However, treatment of lactam **2** with an excess amount (3 equiv.) of methylmagnesium chloride at 5 °C stereoselectively led to the expected 1-substituted tetrahydroisoquinolone **5a** in 61% yield (Table 1).^[10] Isoquinolone **3** was formed as a byproduct (17%). Higher temperatures resulted in the formation of increasing amounts of **3**, whereas when the reaction was carried out at a lower temperature the starting lactam was recovered to a considerable extent.

The observed retention of the configuration of the reactive methine carbon can be rationalized by considering that



Scheme 2. Preparation of key tricyclic lactam **2**.

Table 1. Enantioselective synthesis of 1-substituted tetrahydroisoquinolines.

	R	X	Yield of 5 [%]	Yield of 6 [%]	Yield of 7 [%]
a	Me	Cl	61	85	70
b	Et	Br	82	92	60
c	C ₆ H ₅	Cl	67	–	–
d	3,4-(MeO) ₂ C ₆ H ₃	Br	54	77	69
e	3,4,5-(MeO) ₃ C ₆ H ₂	Br	49	87	58
f	(<i>p</i> -MeO)C ₆ H ₄ CH ₂	Cl	63	85	59
g	C ₆ H ₅ CH ₂ CH ₂	Br	67	79	77
h	CH ₂ =CHCH ₂	Br	42	90	–
i		Br	45	92	–

the Grignard reagent coordinates with the oxygen atom of the oxazolidine ring and that the subsequent intramolecular delivery of the alkyl group occurs on the same face of the C–O bond of the incipient acyl iminium salt (Figure 2).^[11]

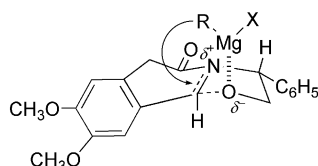


Figure 2. Stereochemical outcome of the α -amidoalkylation reaction.

As in related *cis*-substituted oxazolopiperidones,^[11] minor *cis* lactam **epi-2** was more reluctant to undergo α -amidoalkylation^[12] than *trans* isomer **2** and, upon treatment with MeMgCl, led to isoquinolone **3** as the major product (50%); 2-methyltetrahydroisoquinoline **5a** was formed in low yield (35%).

Removal of the phenylethanol moiety from lactam **5a** was accomplished in excellent yield with sodium in liquid ammonia to give *N*-unsubstituted lactam **6a**. Subsequent reduction with borane generated in situ from NaBH₄ and iodine completed the enantioselective synthesis of (–)-sal-solidine (**7a**).^[13] Taking into account previous correlations, this synthesis also constitutes a formal synthesis of the alkaloid (–)-carnegine.^[14]

The above protocol provides general access to 1-alkyl-substituted tetrahydroisoquinolines. Thus, reaction of lactam **2** with ethylmagnesium bromide stereoselectively afforded (82% yield) lactam **5b**, which was then debenzylated and converted into (*S*)-1-ethyl-1,2,3,4-tetrahydroisoquinoline **7b** in good overall yield, as in the above methyl series.

With the aim of demonstrating the potential of the methodology for the synthesis of 1-aryl-, 1-benzyl-, and 1-phenethyltetrahydroisoquinoline alkaloids, we applied the above three-step sequence from lactam **2** using a variety of aryl-, benzyl-, and phenethylmagnesium halides. The results are summarized in Table 1 (Entries c–g). In all cases the α -amidoalkylation reaction took place stereoselectively to give a single 1-substituted tetrahydroisoquinolone derivative (i.e., **5c–g**).^[15]

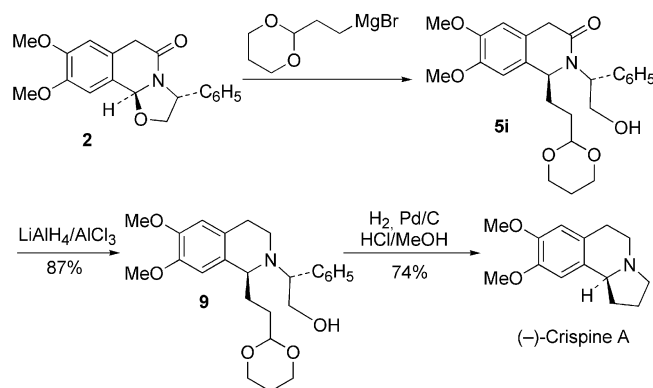
Although the reductive cleavage of the exocyclic benzylic C–N bond of 2-phenyl derivative **5c** with Na/liq. NH₃ occurred with concomitant cleavage of the doubly benzylic endocyclic C–N bond to give 2-benzyl-4,5-dimethoxyphenylacetamide (**8**), a similar reduction from the methoxyphenyl-substituted tetrahydroisoquinolones **5d** and **5e** satisfactorily led to the respective *N*-unsubstituted lactams **6d** and **6e** in excellent yield. Subsequent reduction of the lactam carbonyl of **6d** led to (–)-norcryptostyline II (**7d**), which constitutes a formal synthesis of the alkaloid (+)-cryptostyline II.^[16] Similarly, lactam **6e** was converted into (–)-norcryptostyline III (**7e**), a known precursor of the alkaloid (+)-cryptostyline III.^[17]

The same set of sequential reductions (Na/liq. NH₃ and then NaBH₄/I₂) was used to convert 2-benzyl derivative **5f** into (–)-*O,O*-dimethylcoclaurine (**7f**).^[18] Taking into ac-

count previous transformations, this synthesis also constitutes a formal synthesis of the alkaloids (+)-*O*-methyarlme-pavine,^[18a,18b] zanoxyline,^[19] and (–)-demethylcoclaurine [(–)-higenamine].^[18d]

Similarly, the usefulness of this methodology in the synthesis of 1-phenethyltetrahydroisoquinolines was demonstrated by the preparation of **7g**^[20] from α -amidoalkylation product **5g**.

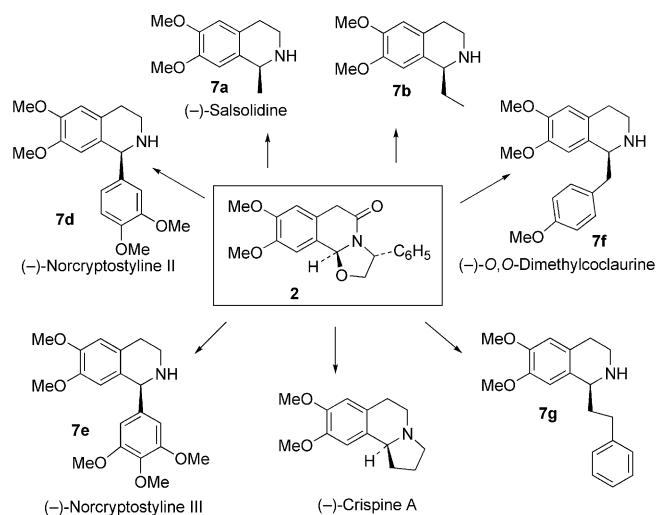
The procedure allows the preparation of tetrahydroisoquinolines and tetrahydroisoquinolones bearing a functionalized C-1 substituent, for instance allyl^[21] or 2-(1,3-dioxan-2-yl)ethyl (Table 1, Entries h and i),^[22] which can open access to more complex tetrahydroisoquinoline alkaloids embodying an additional ring. This was exemplified with the synthesis of the pyrrolo[2,1-*g*]isoquinoline alkaloid crispine A. The three-carbon fragment required for the construction of the pyrrolidine ring was incorporated in the α -amidoalkylation step. Thus, reaction of lactam **2** with the Grignard reagent derived from 2-(2-bromoethyl)-1,3-dioxane (Scheme 3) gave 1-substituted tetrahydroisoquinolone. In this synthesis, the lactam carbonyl was reduced prior to debenzylation to give tetrahydroisoquinoline **9** in excellent yield. Subsequent catalytic hydrogenation under acidic conditions brought about the hydrogenolysis of the exocyclic benzylic C–N bond, deprotection of the acetal function, and closure of the pyrrolidine ring by reductive amination, directly leading to crispine A^[23] in 74% yield.



Scheme 3. Enantioselective synthesis of (–)-crispine A.

Conclusions

Tricyclic (*R*)-phenylglycinol-derived lactam **2** has proven to be a useful scaffold that provides general access to enantiopure 1-substituted tetrahydroisoquinoline derivatives, including 1-alkyl-, 1-aryl-, and 1-benzyltetrahydroisoquinoline alkaloids as well as more complex alkaloids bearing the tetrahydroisoquinoline moiety (Scheme 4). The enantioselective synthesis of 1-benzyltetrahydroisoquinolines is of particular interest because these derivatives not only play a pivotal role in the biosynthesis of numerous alkaloids with a variety of skeletal types (e.g., aporphines, cularines, protoberberines, and pavines) but have also been used as key synthetic precursors of such alkaloids.^[24]



Scheme 4. Enantiopure 1-substituted tetrahydroisoquinolines prepared from common scaffold **2**.

Experimental Section

General: Flash chromatography was carried out on SiO₂ (silica gel 60, SDS, 0.04–0.06 mm) or (when indicated) by using a cartridge containing amine-functionalized silica. Melting points were taken with a Büchi apparatus and are uncorrected. Optical rotations were measured with a Perkin-Elmer 241 polarimeter. High-resolution mass spectra (HMRS; LC/MSD TOF Agilent Technologies) were performed by Serveis Científic-Tècnics, Barcelona. Microanalyses (Carlo Erba 1106 analyzer) were performed by Centre d'Investigació i Desenvolupament (CSIC), Barcelona. Only noteworthy IR absorptions (Perkin-Elmer 1600) are listed. NMR spectra were recorded with either a Varian Gemini-300 (300 and 75.4 MHz for ¹H and ¹³C, respectively) or Mercury-400 (400 and 100.6 MHz for ¹H and ¹³C, respectively) spectrometer.

(3R,10bS)-8,9-Dimethoxy-5-oxo-3-phenyl-2,3,6,10b-tetrahydro-5H-oxazolo[2,3-a]isoquinoline (2): To a mixture of aldehyde-ester **1**^[6] (993 mg, 4.2 mmol) and (*R*)-phenylglycinol (690 mg, 5.0 mmol) in anhydrous toluene (45 mL) containing 4 Å molecular sieves was added a catalytic amount of *p*-TsOH. The mixture was heated at reflux for 18 h with azeotropic elimination of water produced by a Dean–Stark apparatus. The resulting suspension was concentrated under reduced pressure to give a yellow foam. Flash chromatography (Et₂O to EtOAc) afforded lactam **2** (710 mg, 52%) and the 10b-epimer *epi-2* (82 mg, 6%). Data for **2**: White solid; m.p. 135–137 °C (Et₂O). [α]_D²⁵ = –136.6 (*c* = 1.0, CHCl₃). IR (KBr): $\tilde{\nu}$ = 1665 cm^{–1}. ¹H NMR (400 MHz, CDCl₃, 25 °C): δ = 3.52 (d, *J* = 19.2 Hz, 1 H, 6-H), 3.73 (dd, *J* = 19.2, 2.2 Hz, 1 H, 6-H), 3.88 (s, 3 H, OCH₃), 3.91 (s, 3 H, OCH₃), 4.02 (dd, *J* = 9.0, 7.5 Hz, 1 H, 2-H), 4.58 (dd, *J* = 9.0, 7.5 Hz, 1 H, 2-H), 5.38 (t, *J* = 7.5 Hz, 1 H, 3-H), 6.02 (d, *J* = 2.2 Hz, 1 H, 10b-H), 6.66 (s, 1 H, 10-H), 6.99 (s, 1 H, 7-H), 7.35 (m, 5 H, ArH) ppm. ¹³C NMR (100.6 MHz, CDCl₃, 25 °C): δ = 36.9 (C-6), 56.0 (OCH₃), 56.1 (OCH₃), 58.6 (C-3), 72.7 (C-2), 87.8 (C-10b), 107.7 (C-10), 109.8 (C-7), 122.5 (C-6a), 123.1 (C-10a), 126.0 (C-o), 127.7 (C-p), 128.8 (C-m), 139.3 (C-i), 148.4 (C-8), 149.7 (C-9), 166.2 (CO) ppm. HRMS: calcd. for C₁₉H₁₉NO₄ [*M* + *H*]⁺ 326.1386; found 326.1382. C₁₉H₁₉NO₄ (325.36): calcd. C 70.14, H 5.89, N 4.31; found C 70.27, H 5.87, N 4.08. Data for *epi-2*: [α]_D²⁵ = +62.5 (*c* = 1.0, CHCl₃). IR (KBr): $\tilde{\nu}$ = 1667 cm^{–1}. ¹H NMR (300 MHz, CDCl₃, 25 °C): δ = 3.45 (d, *J* = 18.9 Hz, 1 H, 6-H), 3.60 (dd, *J* = 18.9, 2.1 Hz, 1 H, 6-H), 3.90 (s,

3 H, OCH₃), 3.94 (s, 3 H, OCH₃), 4.20 (dd, *J* = 9.0, 0.9 Hz, 1 H, 2-H), 4.47 (dd, *J* = 9.0, 6.3 Hz, 1 H, 2-H), 5.10 (d, *J* = 6.3 Hz, 1 H, 3-H), 5.90 (d, *J* = 2.1 Hz, 1 H, 10b-H), 6.71 (s, 1 H, 10-H), 7.10 (s, 1 H, 7-H), 7.15–7.25 (m, 5 H, ArH) ppm. ¹³C NMR (75.6 MHz, CDCl₃, 25 °C): δ = 38.1 (C-6), 55.9 (OCH₃), 56.0 (OCH₃), 58.6 (C-3), 74.8 (C-2), 87.3 (C-10b), 106.5 (C-10), 110.1 (C-7), 123.0 (C-6a), 125.0 (C-10a), 125.9 (C-o), 127.4 (C-p), 128.4 (C-m), 140.5 (C-i), 148.0 (C-8), 149.2 (C-9), 165.2 (CO) ppm. HRMS: calcd. for C₁₉H₁₉NO₄ [*M* + *H*]⁺ 326.1386; found 326.1382.

Dimer 4: A solution of 1.2 M HCl in MeOH (6 mL) was added to a solution of isoquinolone **3** (96 mg, 0.3 mmol) in MeOH (1 mL). The mixture was heated at reflux for 66 h. The solvent was removed, and the resulting solid was diluted with EtOAc. The solution was washed with saturated aqueous Na₂CO₃. The organic phase was dried and concentrated to give a residue, which was purified by chromatography (7:3 Et₂O/EtOAc to EtOAc) to afford **4** (47 mg, 49%) as a yellow oil. ¹H NMR (400 MHz, CDCl₃, 25 °C): δ = 3.48 (s, 6 H, 2 OCH₃), 3.64 (s, 6 H, 2 OCH₃), 4.27 (dd, *J* = 13.0, 2.8 Hz, 2 H, 2 CH₂OH), 4.43 (d, *J* = 10.8 Hz, 2 H, 2 CHCO), 4.44 (dd, *J* = 13.0, 3.6 Hz, 2 H, 2 CH₂OH), 4.79 (d, *J* = 11.2 Hz, 2 H, 2 CHNCO), 5.68 (s, 2 H, 2 CH₃OCCH), 5.73 (t, *J* = 2.9 Hz, 2 H, CHAr), 6.26 (s, 2 H, 2 CH₃OCCH), 7.08 (d, *J* = 6.4 Hz, 4 H, ArH), 7.14–7.23 (m, 6 H, ArH) ppm. ¹³C NMR (100.6 MHz, CDCl₃, 25 °C): δ = 55.9 (OCH₃), 56.0 (OCH₃), 56.9 (CHCO), 58.5 (CHNCO), 58.7 (CHAr), 62.1 (CH₂OH), 108.6 (CH₃OCCH), 110.3 (CH₃OCCH), 127.7 (C-p), 128.4 (C-o), 128.7 (CCHCO), 128.9 (C-m), 131.5 (CCHN), 136.4 (C-i), 147.5 (CH₃OC), 147.9 (CH₃OC), 176.0 (CO) ppm. HRMS: calcd. for C₃₈H₃₈N₂O₈ [*M* + *H*]⁺ 651.2706; found 651.2697.

General Procedure for the α -Amidoalkylation Reaction: The Grignard reagent (3.0 equiv.) was added to a cooled (5 °C) solution of oxazolopiperidone **2** (1 equiv.) in THF, and the mixture was stirred at this temperature until the disappearance of the starting material was observed by TLC. The reaction was quenched by the addition of water, and the mixture was extracted with EtOAc. The combined extracts were dried and concentrated to give the 1-substituted tetrahydroisoquinolones after flash chromatography.

(1S)-2-[(1R)-2-Hydroxy-1-phenylethyl]-6,7-dimethoxy-1-methyl-3-oxo-1,2,3,4-tetrahydroisoquinoline (5a): Following the above general procedure (reaction time 1.5 h), from lactam **2** (100 mg, 0.31 mmol) and methylmagnesium chloride (3 M in THF, 0.31 mmol) in THF (12.5 mL) a brown oil was obtained. Flash chromatography (7:3 Et₂O/EtOAc, increasing polarity and 9:1 EtOAc/EtOH) gave **5a** (64 mg, 61%) as a yellow oil and isoquinolone **3** (17 mg, 17%) as a yellow-green foam. Data for **5a**: [α]_D²⁵ = +23.5 (*c* = 1.0, CHCl₃). IR (KBr): $\tilde{\nu}$ = 1629, 3400 cm^{–1}. ¹H NMR (400 MHz, CDCl₃, 25 °C): δ = 1.39 (d, *J* = 7.2 Hz, 3 H, CH₃), 3.60 (d, *J* = 18.9 Hz, 1 H, 4-H), 3.76 (d, *J* = 18.9 Hz, 1 H, 4-H), 3.77 (s, 3 H, OCH₃), 3.86 (s, 3 H, OCH₃), 4.28 (q, *J* = 7.2 Hz, 1 H, 1-H), 4.29 (dd, *J* = 12.0, 8.4 Hz, 1 H, CH₂OH), 4.30 (dd, *J* = 12.0, 5.2 Hz, 1 H, CH₂OH), 5.70 (dd, *J* = 8.4, 5.2 Hz, 1 H, CHAr), 6.38 (s, 1 H, 8-H), 6.66 (s, 1 H, 5-H), 7.18–7.30 (m, 5 H, ArH) ppm. ¹³C NMR (100.6 MHz, CDCl₃, 25 °C): δ = 23.2 (CH₃), 37.3 (C-4), 55.6 (OCH₃), 56.0 (OCH₃), 56.1 (C-1), 60.8 (CHAr), 63.3 (CH₂OH), 107.7 (C-8), 110.3 (C-5), 123.1 (C-4a), 127.6 (C-o), 128.1 (C-p), 128.7 (C-m), 130.5 (C-8a), 136.8 (C-i), 148.3 (C-7), 147.8 (C-6), 171.7 (CO) ppm. HRMS: calcd. for C₂₀H₂₃NO₄ [*M* + *H*]⁺ 342.1699; found 342.1695. C₂₀H₂₃NO₄·1/4CH₂Cl₂ (362.64): calcd. C 67.07, H 6.53, N 3.86; found C 67.13, H 6.65, N 3.81. Data for **3**: IR (KBr): $\tilde{\nu}$ = 1652, 3269 cm^{–1}. ¹H NMR (400 MHz, CDCl₃, 25 °C): δ = 3.82 (s, 3 H, OCH₃), 3.85 (s, 3 H, OCH₃), 4.31 (dd, *J* = 12.4, 7.2 Hz, 1 H, CH₂OH), 4.42 (dd, *J* = 12.4, 4.4 Hz, 1 H,

CH₂OH), 6.12 (s, 1 H, 5-H), 6.26 (s, 1 H, 8-H), 6.47 (dd, *J* = 7.2, 4.4 Hz, 1 H, CHAr), 6.59 (s, 1 H, 4-H), 7.33 (m, 5 H, ArH), 7.95 (s, 1 H, 1-H) ppm. ¹³C NMR (100.6 MHz, CDCl₃, 25 °C): δ = 55.7 (OCH₃), 55.8 (OCH₃), 60.7 (CHAr), 62.9 (CH₂OH), 100.6 (C-7), 103.6 (C-5), 107.6 (C-4), 114.2 (C-8a), 127.9 (C-*m*), 128.1 (C-*p*), 128.9 (C-*o*), 135.3 (C-1), 137.4 (C-*i*), 140.6 (C-6), 147.7 (C-7), 155.0 (C-4a), 160.5 (CO) ppm. EM (IQ⁺): *m/z* (%) = 326 (47), 325 (5), 206 (13), 138 (27), 122 (12) 121 (100).

(1S)-1-Ethyl-2-[(1R)-2-hydroxy-1-phenylethyl]-6,7-dimethoxy-3-oxo-1,2,3,4-tetrahydroisoquinoline (5b): Following the general procedure (reaction time 6 h), from lactam **2** (400 mg, 1.23 mmol) in THF (10 mL) and ethylmagnesium bromide (3 M in Et₂O, 1.23 mL, 3.68 mmol) a residue was obtained. Flash chromatography (1:1 Et₂O/EtOAc) gave **5b** (354 mg, 82%) as a yellow oil: $[\alpha]_D^{25} = +34.4$ (*c* = 1.0, CHCl₃). IR (KBr): $\tilde{\nu}$ = 1630, 3388 cm⁻¹. ¹H NMR (400 MHz, CDCl₃, 25 °C): δ = 0.72 (t, *J* = 7.2 Hz, 3 H, CH₃), 1.66–1.77 (m, 1 H, CH₂), 1.79–1.89 (m, 1 H, CH₂), 3.57 (d, *J* = 18.0 Hz, 1 H, 4-H), 3.77 (s, 3 H, OCH₃), 3.79 (d, *J* = 18.0 Hz, 1 H, 4-H), 3.86 (s, 3 H, OCH₃), 4.00 (dd, *J* = 9.6, 3.2 Hz, 1 H, 1-H), 4.23 (dd, *J* = 11.6, 8.4 Hz, 1 H, CH₂OH), 4.29 (dd, *J* = 11.6, 5.2 Hz, 1 H, CH₂OH), 5.66 (dd, *J* = 8.4, 5.2 Hz, 1 H, CHAr), 6.33 (s, 1 H, 8-H), 6.67 (s, 1 H, 5-H), 7.10–7.30 (m, 5 H, ArH) ppm. ¹³C NMR (100.6 MHz, CDCl₃, 25 °C): δ = 10.2 (CH₃), 29.1 (CH₂), 37.5 (C-4), 55.9 (OCH₃), 56.1 (OCH₃), 61.3 (C-1), 61.5 (CHAr), 63.4 (CH₂OH), 109.3 (C-8), 110.3 (C-5), 123.7 (C-4a), 127.7 (C-*o*), 127.8 (C-*p*), 127.8 (C-8a), 129.9 (C-*m*), 136.8 (C-*i*), 147.2 (C-7), 148.3 (C-6), 171.9 (CO) ppm. HRMS: calcd. for C₂₁H₂₅NO₄ [M + H]⁺ 356.1862; found 356.1872. C₂₁H₂₅NO₄·1/4CHCl₃ (385.28): calcd. C 66.25, H 6.61, N 3.64; found C 66.13, H 6.64, N 3.53.

(1S)-2-[(1R)-2-Hydroxy-1-phenylethyl]-6,7-dimethoxy-3-oxo-1-phenyl-1,2,3,4-tetrahydroisoquinoline (5c): Following the general procedure (reaction time 1 h), from lactam **2** (500 mg, 1.54 mmol) in THF (10 mL) and phenylmagnesium chloride (2 M in THF, 2.3 mL, 4.61 mmol) a residue was obtained. Flash chromatography (Et₂O/EtOAc increasing polarity and 9:1 EtOAc/EtOH) gave **5c** (415 mg, 67%) as a yellow oil and **3** (125 mg, 25%). Data for **5c**: $[\alpha]_D^{25} = +16.7$ (*c* = 1.0, CHCl₃). IR (KBr): $\tilde{\nu}$ = 1629, 3388 cm⁻¹. ¹H NMR (300 MHz, CDCl₃, 25 °C): δ = 3.66 (d, *J* = 19.8 Hz, 1 H, 4-H), 3.71 (s, 3 H, OCH₃), 3.80 (s, 3 H, OCH₃), 3.84 (d, *J* = 19.8 Hz, 1 H, 4-H), 3.88–3.91 (m, 2 H, CH₂OH), 5.26 (s, 1 H, 1-H), 5.96 (t, *J* = 6.6 Hz, 1 H, CHAr), 6.41 (s, 1 H, 8-H), 6.58 (s, 1 H, 5-H), 7.15–7.30 (m, 10 H, ArH) ppm. ¹³C NMR (75.4 MHz, CDCl₃, 25 °C): δ = 37.2 (C-4), 55.8 (OCH₃), 55.9 (OCH₃), 59.9 (C-1), 62.2 (CH₂OH), 62.5 (CHAr), 108.6 (C-8), 110.0 (C-5), 122.3 (C-4a), 126.0 (C-*o*), 127.4 (C-*p*), 127.8 (C-*p*), 128.1 (C-*m*), 128.3 (C-*o*), 128.5 (C-8a), 128.8 (C-*m*), 136.7 (C-*i*), 143.0 (C-*i*), 147.8 (C-6), 148.0 (C-7), 171.9 (CO) ppm. HRMS: calcd. for C₂₅H₂₅NO₄ [M + H]⁺ 404.1862; found 404.1875.

(1S)-1-(3,4-Dimethoxyphenyl)-2-[(1R)-2-hydroxy-1-phenylethyl]-6,7-dimethoxy-3-oxo-1,2,3,4-tetrahydroisoquinoline (5d): Following the general procedure (reaction time 15 min), from lactam **2** (150 mg, 0.46 mmol) in THF (10 mL) and 3,4-dimethoxyphenylmagnesium bromide (0.5 M in THF, 2.8 mL, 1.4 mmol) a residue was obtained. Flash chromatography (1:1 Et₂O/EtOAc, increasing polarity and 9:1 EtOAc/EtOH) gave **5d** (115 mg, 54%) as a yellow foam and **3** (50 mg, 33%). Data for **5d**: $[\alpha]_D^{25} = +17.1$ (*c* = 1.0, CHCl₃). IR (KBr): $\tilde{\nu}$ = 1634, 3406 cm⁻¹. ¹H NMR (400 MHz, CDCl₃, 25 °C): δ = 3.68 (d, *J* = 20.0 Hz, 1 H, 4-H), 3.73 (s, 3 H, OCH₃), 3.79 (s, 3 H, OCH₃), 3.83 (s, 3 H, CH₃O), 3.86 (s, 3 H, CH₃O), 3.87 (d, *J* = 20.0 Hz, 1 H, 4-H), 3.95 (dd, *J* = 11.6, 8.4 Hz, 1 H, CH₂OH), 4.01 (dd, *J* = 11.6, 5.2 Hz, 1 H, CH₂OH), 5.18 (s, 1 H, 1-H), 5.93 (dd, *J* = 8.4, 5.2 Hz, 1 H, CHAr), 6.37 (s, 1 H, 2'-H), 6.58 (s, 1 H,

5'-H), 6.72 (s, 1 H, 6'-H), 6.75 (s, 1 H, 8-H), 6.76 (s, 1 H, 5-H), 7.12–7.15 (m, 2 H, ArH), 7.26–7.32 (m, 3 H, ArH) ppm. ¹³C NMR (100.6 MHz, CDCl₃, 25 °C): δ = 37.4 (C-4), 55.8 (OCH₃), 55.9 (OCH₃), 55.9 (OCH₃), 56.0 (OCH₃), 60.4 (C-1), 62.5 (CHAr), 62.6 (CH₂OH), 108.1 (C-8), 109.5 (C-5), 110.1 (C-2'), 111.3 (C-5'), 118.3 (C-6'), 122.4 (C-4a), 127.9 (C-*p*), 128.4 (C-*o*), 128.6 (C-8a), 128.6 (C-*m*), 134.4 (C-1'), 136.2 (C-*i*), 147.9 (C-6), 148.5 (C-4'), 148.6 (C-7), 149.2 (C-3'), 171.6 (CO) ppm. HRMS: calcd. for C₂₇H₂₉NO₆ [M + H]⁺ 464.2073; found 464.2081. C₂₇H₂₉NO₆·1/4CHCl₃ (493.37): calcd. C 66.34, H 5.98, N 2.84; found C 66.65, H 6.33, N 2.49.

(1S)-2-[(1R)-2-Hydroxy-1-phenylethyl]-6,7-dimethoxy-3-oxo-1-(3,4,5-trimethoxyphenyl)-1,2,3,4-tetrahydroisoquinoline (5e): Following the general procedure (reaction time 20 min), from lactam **2** (500 mg, 1.54 mmol) in THF (10 mL) and 3,4,5-trimethoxyphenylmagnesium bromide (0.5 M in THF, 9.2 mL, 4.61 mmol) a residue was obtained. Flash chromatography (Et₂O/EtOAc, increasing polarity and 9:1 EtOAc/EtOH) gave **5e** (370 mg, 49%) as a yellow foam and **3** (135 mg, 27%). Data for **5e**: $[\alpha]_D^{25} = +13.1$ (*c* = 1.0, CHCl₃). IR (KBr): $\tilde{\nu}$ = 1684, 2930 cm⁻¹. ¹H NMR (300 MHz, CDCl₃, 25 °C): δ = 3.65 (d, *J* = 19.5 Hz, 1 H, 4-H), 3.75 (s, 3 H, OCH₃), 3.77 (s, 3 H, OCH₃), 3.79 (s, 3 H, OCH₃), 3.80 (masked d, 4-H), 3.81 (s, 3 H, OCH₃), 3.85 (s, 3 H, OCH₃), 5.17 (s, 1 H, 1-H), 3.98–4.08 (m, 2 H, CH₂OH), 5.89 (dd, *J* = 8.7, 5.1 Hz, 1 H, CHAr), 6.40 (s, 1 H, 2'-H), 6.46 (s, 2 H, 5-H, 8-H), 6.62 (s, 2 H, 6'-H), 7.13–7.27 (m, 2 H, ArH), 7.29–7.31 (m, 3 H, ArH) ppm. ¹³C NMR (100.6 MHz, CDCl₃, 25 °C): δ = 37.3 (C-4), 55.8 (OCH₃), 55.9 (OCH₃), 56.0 (OCH₃), 56.1 (OCH₃), 56.2 (OCH₃), 60.8 (C-1), 62.8 (CH₂OH), 63.0 (CHAr), 103.3 (C-2', C-6'), 108.1 (C-8), 110.0 (C-5), 122.7 (C-4a), 128.1 (C-*p*), 128.4 (C-*o*), 128.6 (C-8a), 128.6 (C-*m*), 136.1 (C-1'), 137.0 (C-*i*), 137.4 (C-4'), 147.9 (C-6), 148.6 (C-7), 153.4 (C-5', C-3'), 172.0 (CO) ppm. HRMS: calcd. for C₂₈H₃₁NO₇ [M + H]⁺ 494.2179; found 494.2183. C₂₈H₃₁NO₇·1/4CHCl₃ (523.40): calcd. C 64.83, H 6.02, N 2.68; found C 64.69, H 6.26, N 2.42.

(1S)-[(R)-2-Hydroxy-1-phenylethyl]-6,7-dimethoxy-1-(*p*-methoxybenzyl)-3-oxo-1,2,3,4-tetrahydroisoquinoline (5f): Following the general procedure (reaction time 15 min), from lactam **2** (150 mg, 0.46 mmol) in THF (10 mL) and 4-methoxybenzylmagnesium chloride (0.25 M in THF, 5.5 mL, 1.4 mmol) a residue was obtained. Flash chromatography (3:7 hexane/EtOAc, increasing polarity and 9:1 EtOAc/EtOH) gave **5f** (129 mg, 63%) as a white foam and **3** (37 mg, 25%). Data for **5f**: $[\alpha]_D^{25} = +41.5$ (*c* = 1.0, CHCl₃). IR (KBr): $\tilde{\nu}$ = 1630, 3393 cm⁻¹. ¹H NMR (400 MHz, CDCl₃, 25 °C): δ = 2.84 (dd, *J* = 13.1, 8.5 Hz, 1 H, CHCH₂Ar), 3.06 (dd, *J* = 13.1, 3.4 Hz, 1 H, CHCH₂Ar), 3.10 (d, *J* = 19.4 Hz, 1 H, 4-H), 3.39 (d, *J* = 19.4 Hz, 1 H, 4-H), 3.51 (s, 3 H, OCH₃C-4'), 3.69 (s, 3 H, OCH₃), 3.82 (s, 3 H, OCH₃), 4.29 (dd, *J* = 8.5, 3.4 Hz, 1 H, 1-H), 4.35–4.44 (m, 2 H, CH₂OH), 5.80 (s, 1 H, 5-H or 8-H), 5.85 (t, *J* = 6.5 Hz, 1 H, CHAr), 6.53 (s, 1 H, 5-H or 8-H), 6.62 (s, 4 H, 2'-H, 3'-H, 5'-H, 6'-H), 7.25–7.35 (m, 5 H, ArH) ppm. ¹³C NMR (75.4 MHz, CDCl₃, 25 °C): δ = 37.2 (C-4), 41.9 (C-1CH₂), 55.2 (OCH₃), 55.8 (OCH₃), 55.9 (OCH₃), 61.4 (C-1), 61.6 (CHAr), 63.6 (CH₂OH), 109.2 (C-8), 109.7 (C-5), 113.5 (C-2', C-6'), 124.2 (C-4a), 127.2 (C-8a), 127.9 (C-*o*), 128.0 (C-*p*), 128.8 (C-*m*), 131.1 (C-*m*), 131.1 (C-3', C-5'), 136.9 (C-*i*), 146.8 (C-6), 148.2 (C-7), 158.5 (C-4'), 172.3 (CO) ppm. HRMS: calcd. for C₂₇H₂₉NO₅ [M + H]⁺ 448.2124; found 448.2130. C₂₇H₂₉NO₅·3/4H₂O (461.04): calcd. C 70.34, H 6.67, N 3.04; found C 70.03, H 6.42, N 2.87.

(1S)-2-[(1R)-2-Hydroxy-1-phenylethyl]-6,7-dimethoxy-3-oxo-1-phenethyl-1,2,3,4-tetrahydroisoquinoline (5g): Following the general procedure (reaction time 40 min), from lactam **2** (400 mg,

1.23 mmol) in THF (10 mL) and phenethylmagnesium chloride (1 M in THF, 3.69 mL, 3.69 mmol) a residue was obtained. Flash chromatography (8:2 Et₂O/EtOAc, increasing polarity and 9:1 EtOAc/EtOH) gave **5g** (353 mg, 67%) as a white foam and **3** (68 mg, 17%). Data for **5g**: $[a]_D^{25} = +72.9$ ($c = 1.0$, CHCl₃). IR (KBr): $\tilde{\nu} = 1632, 3399 \text{ cm}^{-1}$. ¹H NMR (400 MHz, CDCl₃, 25 °C): $\delta = 1.92\text{--}2.07$ (m, 1 H, CH₂), 2.10–2.18 (m, 1 H, CH₂), 2.25–2.36 (m, 1 H, CH₂Ar), 2.50–2.57 (m, 1 H, CH₂Ar), 3.59 (d, $J = 18.8 \text{ Hz}$, 1 H, 4-H), 3.78 (s, 3 H, OCH₃), 3.81 (d, $J = 18.8 \text{ Hz}$, 1 H, 4-H), 3.87 (s, 3 H, OCH₃), 4.10 (dd, $J = 9.2, 2.8 \text{ Hz}$, 1 H, 1-H), 4.18–4.23 (m, 2 H, CH₂OH), 5.59 (dd, $J = 7.6, 6.0 \text{ Hz}$, 1 H, CHAr), 6.34 (s, 1 H, 8-H), 6.69 (s, 1 H, 5-H), 7.01 (d, $J = 13.2 \text{ Hz}$, 2 H, C-2', C-6'), 7.15 (m, 1 H, 4'-H), 7.20 (br. s, 2 H, C-3', C-5'), 7.24–7.26 (m, 5 H, ArH) ppm. ¹³C NMR (100.6 MHz, CDCl₃, 25 °C): $\delta = 31.5$ (CH₂Ar), 37.6 (C-4), 37.7 (CH₂), 56.0 (OCH₃), 56.1 (OCH₃), 59.4 (C-1), 61.7 (CHAr), 63.3 (CH₂OH), 109.1 (C-8), 110.5 (C-5), 123.9 (C-4a), 126.1 (C-4'), 127.8 (C-p), 127.8 (C-m), 128.1 (C-o), 128.3 (C-8a), 128.5 (C-2', C-6'), 128.6 (C-3', C-5'), 136.7 (C-i), 140.6 (C-1'), 147.3 (C-6), 148.4 (C-7), 171.9 (CO) ppm. HRMS: calcd. for C₂₇H₂₉NO₄ [M + H]⁺ 432.2175; found 432.2180. C₂₇H₂₉NO₄·3/4H₂O (445.04): calcd. C 72.87, H 6.91, N 3.15; found C 72.95, H 6.87, N 2.95.

(1S)-1-Allyl-2-[(1R)-2-hydroxy-1-phenylethyl]-6,7-dimethoxy-3-oxo-1,2,3,4-tetrahydroisoquinoline (5h): Following the general procedure (reaction time 2 h), from lactam **2** (200 mg, 0.6 mmol) in THF (10 mL) and allylmagnesium bromide (1 M in Et₂O, 1.85 mL, 1.85 mmol) a yellow oil was obtained. Flash chromatography (95:5 *tert*-butyl methyl ether/EtOAc) gave **5h** (92 mg, 42%) as a white oil and 1-(2-allyl-2-hydroxy-4-pentenyl)-2-[1-[2-hydroxy-(1R)-phenylethylamino]-3-butenyl]-4,5-dimethoxybenzene (**10**; 103 mg, 39%). Data for **5h**: $[a]_D^{25} = +16.8$ ($c = 1.0$, CHCl₃). IR (KBr): $\tilde{\nu} = 1637, 3386 \text{ cm}^{-1}$. ¹H NMR (300 MHz, CDCl₃, 25 °C): $\delta = 2.18\text{--}2.33$ (m, 1 H, CH₂CH=), 2.39–2.60 (m, 1 H, CH₂CH=), 3.54 (d, $J = 19.5 \text{ Hz}$, 1 H, 4-H), 3.79 (d, $J = 19.5 \text{ Hz}$, 1 H, 4-H), 3.76 (s, 3 H, OCH₃), 3.86 (s, 3 H, OCH₃), 4.26 (m, 1 H, 1-H), 4.28 (dd, $J = 11.4, 7.8 \text{ Hz}$, 1 H, CH₂OH), 4.30 (dd, $J = 11.4, 5.7 \text{ Hz}$, 1 H, CH₂OH), 4.90 (dd, $J = 10.5, 1.8 \text{ Hz}$, 1 H, CH₂=), 4.99 (td, $J = 6.0, 1.8 \text{ Hz}$, 1 H, CH₂=), 5.51 (m, 1 H, CH=), 5.68 (dd, $J = 7.8, 5.7 \text{ Hz}$, 1 H, 1-H), 6.31 (s, 1 H, 8-H), 6.65 (s, 1 H, 5-H), 7.22–7.38 (m, 5 H, ArH) ppm. ¹³C NMR (75.4 MHz, CDCl₃, 25 °C): $\delta = 37.6$ (C-4), 40.8 (CH₂CH=), 55.8 (OCH₃), 56.0 (OCH₃), 60.1 (C-1), 61.3 (CHAr), 63.2 (CH₂OH), 109.0 (C-8), 110.0 (C-5), 118.9 (CH₂=), 123.6 (C-4a), 127.6 (C-p), 127.7 (C-o), 128.4 (C-m), 128.6 (C-8a), 133.0 (CH=), 136.8 (C-i), 147.1 (C-7), 148.2 (C-6), 171.8 (CO) ppm. HRMS: calcd. for C₂₂H₂₅NO₄ [M + H]⁺ 368.1862; found 368.1873. C₂₂H₂₅NO₄·1/2H₂O (411.5): calcd. C 70.05, H 7.10, N 3.40; found C 66.69, H 6.70, N 3.55. Data for **10**: IR (KBr): $\tilde{\nu} = 1638, 3073, 3324 \text{ cm}^{-1}$. ¹H NMR (400 MHz, CDCl₃, 25 °C): $\delta = 2.10\text{--}2.19$ (m, 4 H, 2 CH₂CHCH₂), 2.38–2.53 (m, 2 H, CHCH₂CHCH₂), 2.56 (d, $J = 14.8 \text{ Hz}$, 1 H, CH₂Ar), 2.66 (d, $J = 14.8 \text{ Hz}$, 1 H, CH₂Ar), 3.57 (dd, $J = 10.8, 8.0 \text{ Hz}$, 1 H, CH₂OH), 3.67 (dd, $J = 10.8, 4.4 \text{ Hz}$, 1 H, CH₂OH), 3.85 (s, 3 H, OCH₃), 3.86 (dd, $J = 8.0, 4.4 \text{ Hz}$, 1 H, CHAr), 3.89 (s, 3 H, OCH₃), 4.05 (t, $J = 6.4 \text{ Hz}$, 1 H, CHCH₂CHCH₂), 4.98–5.09 (m, 2 H, CHCH₂CHCH₂), 5.10–5.15 (m, 4 H, 2 CH₂CHCH₂), 5.64–5.72 (m, 1 H, CHCH₂CHCH₂), 5.74–5.84 (m, 2 H, 2 CH₂CHCH₂), 6.65 (s, 1 H, CH₃OCCH), 6.85 (s, 1 H, CH₃OCCH), 7.26–7.28 (m, 5 H, ArH) ppm. ¹³C NMR (75.4 MHz, CDCl₃, 25 °C): $\delta = 40.3$ (CHCH₂CHCH₂), 40.4 (CH₂Ar), 43.7 (CH₂CHCH₂), 44.0 (CH₂CHCH₂), 55.1 (CHCH₂CHCH₂), 55.6 (OCH₃), 55.7 (OCH₃), 61.5 (CHAr), 66.3 (CH₂OH), 73.3 (COH), 110.1 (C-3), 114.8 (C-6), 117.3 (CHCH₂CHCH₂), 118.5 (CH₂CHCH₂), 118.6 (CH₂CHCH₂), 127.0 (C-2), 127.3 (C-m), 127.4 (C-p), 128.4 (C-o), 133.8 (CH₂CHCH₂),

133.9 (CH₂CHCH₂), 135.0 (C-1), 135.2 (CHCH₂CHCH₂), 140.9 (C-i), 146.9 (C-4), 147.5 (C-5) ppm. HRMS: calcd. for C₂₈H₃₇NO₄ [M + H]⁺ 452.2801; found 452.2784. C₂₈H₃₇NO₄·1/2H₂O (460.61): calcd. C 73.01, H 8.32, N 3.04; found C 73.24, H 8.13, N 2.75.

(1S)-1-[2-(1,3-Dioxan-2-yl)ethyl]-2-[(1R)-2-hydroxy-1-phenylethyl]-6,7-dimethoxy-3-oxo-1,2,3,4-tetrahydroisoquinoline (5i): Following the general procedure (reaction time 2.5 h), from lactam **2** (400 mg, 1.23 mmol) in THF (20 mL) and 2-(1,3-dioxan-2-yl)ethylmagnesium bromide (0.5 M in THF, 7.4 mL, 3.69 mmol) a yellow solid was obtained. Flash chromatography (1:1 Et₂O/EtOAc, increasing polarity and 9:1 EtOAc/EtOH) gave **5i** (246 mg, 45%) as a yellow foam and **3** (121 mg, 30%). Data for **5i**: $[a]_D^{25} = +38.5$ ($c = 1.0$, CHCl₃). IR (KBr): $\tilde{\nu} = 1632, 3399 \text{ cm}^{-1}$. ¹H NMR (400 MHz, CDCl₃, 25 °C): $\delta = 1.31$ (dt, $J = 13.6, 1.2 \text{ Hz}$, 2 H, 1'-H), 1.41–1.46 (m, 2 H, OCH₂CH₂), 1.72–1.81 (m, 1 H, 2'-H), 1.92–2.06 (m, 1 H, 2'-H), 3.56 (d, $J = 19.0 \text{ Hz}$, 1 H, 4-H), 3.68 (ddd, $J = 15.2, 12.0, 3.6 \text{ Hz}$, 2 H, CH₂CH₂O), 3.75 (s, 3 H, OCH₃), 3.79 (d, $J = 19.0 \text{ Hz}$, 1 H, 4-H), 3.85 (s, 3 H, OCH₃), 4.03 (m, 2 H, CH₂CH₂O), 4.40 (t, $J = 4.8 \text{ Hz}$, 1 H, CHO₂), 4.15 (dd, $J = 10.0, 3.2 \text{ Hz}$, 1 H, 1-H), 4.23–4.32 (m, 2 H, CH₂OH), 5.76 (dd, $J = 8.0, 5.6 \text{ Hz}$, 1 H, CHAr), 6.34 (s, 1 H, 8-H), 6.65 (s, 1 H, 5-H), 7.16 (d, $J = 1.6 \text{ Hz}$, 1 H, ArH), 7.18 (d, $J = 2.0 \text{ Hz}$, 1 H, ArH), 7.25–7.30 (m, 3 H, ArH) ppm. ¹³C NMR (100.6 MHz, CDCl₃, 25 °C): $\delta = 25.6$ (C-1'), 30.3 (C-2'), 31.1 (CH₂CH₂O), 37.6 (C-4), 55.9 (OCH₃), 56.0 (OCH₃), 58.9 (C-1), 60.3 (CHAr), 63.1 (CH₂OH), 66.7 (2 CH₂CH₂O), 101.6 (CHO₂), 109.4 (C-8), 110.4 (C-5), 123.8 (C-4a), 127.7 (C-p), 127.8 (C-o), 128.1 (C-8a), 128.5 (C-m), 136.8 (C-i), 147.2 (C-6), 148.3 (C-7), 171.9 (CO) ppm. HRMS: calcd. for C₂₅H₃₁NO₆ [M + H]⁺ 442.2223; found 442.2219.

General Procedure for Na/liq. NH₃ Reaction: Into a three-necked, round-bottomed flask equipped with a cold-finger condenser charged with dry ice/acetone was condensed NH₃ at –78 °C. The temperature was raised to –33 °C, and a solution of lactam **5** in THF was added. Then, sodium metal was added in small portions until the blue color persisted. After the mixture was stirred at –33 °C for 1 min, the reaction was quenched by the addition of solid NH₄Cl until the blue color disappeared. The mixture was stirred at room temperature for 4 h, poured into water, and extracted with Et₂O. The combined organic extracts were dried and concentrated to give a residue, which was purified by chromatography.

(1S)-6,7-Dimethoxy-1-methyl-3-oxo-1,2,3,4-tetrahydroisoquinoline (6a): Operating as described in the general procedure, from **5a** (200 mg, 0.59 mmol) in THF (7 mL) and NH₃ (50 mL) a clear maroon residue was obtained. Flash chromatography (9:1 EtOAc/EtOH) afforded **6a** (110 mg, 85%) as a white solid. $[a]_D^{25} = +10.0$ ($c = 1.0$, CHCl₃). IR (KBr): $\tilde{\nu} = 1668, 3217 \text{ cm}^{-1}$. ¹H NMR (400 MHz, CDCl₃, 25 °C): $\delta = 1.51$ (d, $J = 6.4 \text{ Hz}$, 3 H, CH₃), 3.48 (d, $J = 20.0 \text{ Hz}$, 1 H, 4-H), 3.60 (d, $J = 20.0 \text{ Hz}$, 1 H, 4-H), 3.87 (s, 6 H, 2 OCH₃), 4.60 (m, 1 H, 1-H), 6.60 (s, 1 H, 8-H), 6.61 (s, 1 H, 5-H), 6.90 (br. s, 1 H, NH) ppm. ¹³C NMR (100.6 MHz, CDCl₃, 25 °C): $\delta = 24.4$ (CH₃), 35.4 (C-4), 51.3 (C-1), 56.0 (OCH₃), 56.1 (OCH₃), 108.2 (C-8), 110.4 (C-5), 122.8 (C-4a), 127.8 (C-8a), 148.0 (C-6), 148.4 (C-7), 171.5 (CO) ppm. HRMS: calcd. for C₁₂H₁₅NO₃ [M + H]⁺ 222.1124; found 222.1122. C₁₂H₁₅NO₃ (221.25): calcd. C 65.14, H 6.83, N 6.33; found C 64.89, H 6.76, N 6.16.

(1S)-1-Ethyl-6,7-dimethoxy-3-oxo-1,2,3,4-tetrahydroisoquinoline (6b): Operating as described in the general procedure, from **5b** (230 mg, 0.65 mmol) in THF (4 mL) and NH₃ (30 mL) a residue was obtained. Flash chromatography (EtOAc) afforded **6b** (140 mg, 92%) as a white oil. $[a]_D^{25} = +21.7$ ($c = 0.57$, CHCl₃). IR (KBr): $\tilde{\nu} = 1654, 2972 \text{ cm}^{-1}$. ¹H NMR (400 MHz, CDCl₃, 25 °C): $\delta = 0.92$

(t, $J = 8.0$ Hz, 3 H, CH₃), 1.81 (m, 2 H, CH₂), 3.46 (d, $J = 20.0$ Hz, 1 H, 4-H), 3.62 (d, $J = 20.0$ Hz, 1 H, 4-H), 3.87 (s, 6 H, 2 OCH₃), 4.44 (m, 1 H, 1-H), 6.60 (s, 1 H, 8-H), 6.62 (s, 1 H, 5-H), 7.70 (br. s, 1 H, NH) ppm. ¹³C NMR (100.6 MHz, CDCl₃, 25 °C): $\delta = 9.1$ (CH₃), 31.7 (CH₂), 35.2 (C-4), 55.9 (OCH₃), 56.0 (OCH₃), 57.2 (C-1), 108.8 (C-8), 110.3 (C-5), 123.2 (C-4a), 126.2 (C-8a), 147.8 (C-7), 148.4 (C-6), 171.9 (CO) ppm. HRMS: calcd. for C₁₃H₁₇NO₃ [M + H]⁺ 236.1286; found 236.1280.

(1S)-1-[3,4-(Dimethoxyphenyl)]-6,7-dimethoxy-3-oxo-1,2,3,4-tetrahydroisoquinoline (6d): Operating as described in the general procedure, from **5d** (215 mg, 0.46 mmol) in THF (3 mL) and NH₃ (35 mL) a residue was obtained. Flash chromatography (2:8 to 1:9 hexane/EtOAc) afforded **6d** (121 mg, 77%) as a yellow foam. IR (KBr): $\tilde{\nu} = 1647, 2920$ cm⁻¹. ¹H NMR (400 MHz, CDCl₃, 25 °C): $\delta = 3.52$ (d, $J = 24.0$ Hz, 1 H, 4-H), 3.66 (d, $J = 24.0$ Hz, 1 H, 4-H), 3.71 (s, 3 H, OCH₃), 3.82 (s, 3 H, OCH₃), 3.86 (s, 3 H, OCH₃), 3.89 (s, 3 H, OCH₃), 5.54 (s, 1 H, 1-H), 6.37 (s, 1 H, 2'-H), 6.65 (s, 1 H, 5'-H), 6.72 (s, 1 H, 6'-H), 6.83 (s, 1 H, 8-H), 6.84 (s, 1 H, 5-H), 7.05 (br. s, 1 H, NH) ppm. ¹³C NMR (100.6 MHz, CDCl₃, 25 °C): $\delta = 35.5$ (C-4), 55.6 (OCH₃), 55.7 (OCH₃), 55.8 (OCH₃), 59.6 (C-1), 109.5 (C-8), 110.0 (C-5), 110.1 (C-2'), 110.9 (C-5'), 119.7 (C-6'), 123.0 (C-4a), 126.1 (C-8a), 134.2 (C-1'), 147.7 (C-6), 148.5 (C-4'), 148.8 (C-7), 149.3 (C-3'), 170.8 (CO) ppm. HRMS: calcd. for C₁₉H₂₁NO₅ [M + H]⁺ 344.1498; found 344.1491.

(1S)-6,7-Dimethoxy-3-oxo-1-[3,4,5-(trimethoxyphenyl)]-1,2,3,4-tetrahydroisoquinoline (6e): Operating as described in the general procedure, from **5e** (150 mg, 0.30 mmol) in THF (2 mL) and NH₃ (30 mL) a residue was obtained. Flash chromatography (EtOAc) afforded **6e** (98 mg, 87%) as a yellow foam. IR (KBr): $\tilde{\nu} = 1663, 2926$ cm⁻¹. ¹H NMR (300 MHz, CDCl₃, 25 °C): $\delta = 3.56$ (d, $J = 18.0$ Hz, 1 H, 4-H), 3.71 (d, $J = 18.0$ Hz, 1 H, 4-H), 3.72 (s, 3 H, OCH₃), 3.76 (s, 3 H, OCH₃), 3.79 (s, 3 H, OCH₃), 3.83 (s, 3 H, OCH₃), 3.84 (s, 3 H, OCH₃), 5.25 (s, 1 H, 1-H), 6.41 (s, 2 H, 2'-H, 6'-H), 6.66 (s, 1 H, 8-H), 6.73 (s, 1 H, 5-H), 7.25 (br. s, 1 H, NH) ppm. ¹³C NMR (75.4 MHz, CDCl₃, 25 °C): $\delta = 38.8$ (C-4), 55.8 (OCH₃), 55.9 (OCH₃), 56.0 (OCH₃), 56.1 (OCH₃), 60.0 (C-1), 60.1 (OCH₃), 104.3 (C-8), 105.4 (C-2', C-6'), 113.9 (C-5), 125.4 (C-4a), 131.2 (C-4'), 131.3 (C-8a), 133.4 (C-1'), 147.7 (C-6), 148.1 (C-7), 153.1 (C-3', C-5'), 173.7 (CO) ppm. HRMS: calcd. for C₂₀H₂₃NO₆ [M + H]⁺ 374.1603; found 374.1592.

(1S)-6,7-Dimethoxy-1-(*p*-methoxybenzyl)-3-oxo-1,2,3,4-tetrahydroisoquinoline (6f): Operating as described in the general procedure, from **5f** (95 mg, 0.21 mmol) in THF (2 mL) and NH₃ (30 mL) a residue was obtained. Flash chromatography (EtOAc to 95:5 EtOAc/EtOH) afforded **6f** (58 mg, 85%) as a yellow foam. $[\alpha]_D^{25} = -61.2$ ($c = 0.5$, CHCl₃). IR (KBr): $\tilde{\nu} = 1630, 2934$ cm⁻¹. ¹H NMR (400 MHz, CDCl₃, 25 °C): $\delta = 2.87$ (d, $J = 20.0$ Hz, 1 H, 4-H), 2.91 (dd, $J = 13.5, 6.0$ Hz, 1 H, CH₂), 3.03 (dd, $J = 13.5, 4.0$ Hz, 1 H, CH₂), 3.23 (d, $J = 20.0$ Hz, 1 H, 4-H), 3.77 (s, 1 H, OCH₃), 3.83 (s, 1 H, OCH₃), 3.86 (s, 1 H, OCH₃), 4.68 (m, 1 H, 1-H), 6.49 (s, 1 H, 8-H), 6.55 (s, 1 H, 5-H), 6.76 (d, $J = 8.2$ Hz, 2 H, 2'-H), 6.86 (d, $J = 8.2$ Hz, 2 H, 3'-H), 6.95 (br. s, 1 H, NH) ppm. ¹³C NMR (100.6 MHz, CDCl₃, 25 °C): $\delta = 35.0$ (C-4), 44.5 (CH₂), 55.2 (OCH₃), 55.9 (C-1), 56.0 (OCH₃), 57.3 (OCH₃), 108.9 (C-8), 110.1 (C-5), 113.8 (C-3'), 123.9 (C-4a), 125.2 (C-2'), 127.8 (C-8a), 131.8 (C-1'), 147.7 (C-6), 148.4 (C-7), 158.5 (C-4'), 172.3 (CO) ppm. HRMS: calcd. for C₁₉H₂₁NO₄ [M + H]⁺ 328.1549; found 328.1532.

(1S)-6,7-Dimethoxy-3-oxo-1-phenethyl-1,2,3,4-tetrahydroisoquinoline (6g): Operating as described in the general procedure, from **5g** (100 mg, 0.23 mmol) in THF (2 mL) and NH₃ (25 mL) a residue was obtained. Flash chromatography (EtOAc) afforded **6g** (56 mg, 79%) as a white foam. $[\alpha]_D^{25} = +16.0$ ($c = 1.0$, CHCl₃). IR (KBr):

$\tilde{\nu} = 1674$ cm⁻¹. ¹H NMR (400 MHz, CDCl₃, 25 °C): $\delta = 2.03$ –2.09 (m, 2 H, CH₂), 2.62–2.70 (m, 2 H, CH₂Ar), 3.48 (d, $J = 20.0$ Hz, 1 H, 4-H), 3.64 (d, $J = 20.0$ Hz, 1 H, 4-H), 3.86 (s, 3 H, OCH₃), 3.87 (s, 3 H, OCH₃), 4.60 (m, 1 H, 1-H), 6.60 (s, 2 H, 5-H, 8-H), 7.14–7.19 (m, 3 H, ArH), 7.25–7.28 (m, 2 H, ArH), 7.43 (m, 1 H, NH) ppm. ¹³C NMR (100.6 MHz, CDCl₃, 25 °C): $\delta = 31.2$ (CH₂Ar), 35.4 (C-4), 40.5 (CH₂), 55.7 (C-1), 56.0 (OCH₃), 56.1 (OCH₃), 108.7 (C-8), 110.5 (C-5), 123.2 (C-4a), 126.1 (C-8a), 126.3 (C-4'), 128.3 (C-3'), 128.5 (C-2'), 140.9 (C-1'), 147.9 (C-6), 148.5 (C-7), 171.7 (CO) ppm. HRMS: calcd. for C₁₉H₂₁NO₃ [M + H]⁺ 312.1599; found 312.1598.

(1S)-1-Allyl-6,7-dimethoxy-3-oxo-1,2,3,4-tetrahydroisoquinoline (6h): Operating as described in the general procedure, from **5h** (80 mg, 0.22 mmol) in THF (2 mL) and NH₃ (25 mL) a residue was obtained. Flash chromatography (EtOAc) afforded **6h** (48.3 mg, 90%) as a yellow foam. $[\alpha]_D^{25} = -10.5$ ($c = 0.6$, CHCl₃). IR (KBr): $\tilde{\nu} = 1667, 2918$ cm⁻¹. ¹H NMR (400 MHz, CDCl₃, 25 °C): $\delta = 2.45$ (ddd, $J = 14.0, 7.2, 7.2$ Hz, 1 H, CH₂), 2.57–2.61 (m, 1 H, CH₂), 3.47 (d, $J = 20.0$ Hz, 1 H, 4-H), 3.60 (d, $J = 20.0$ Hz, 1 H, 4-H), 3.88 (s, 6 H, 2 OCH₃), 4.52 (m, 1 H, 1-H), 5.12–5.17 (m, 2 H, =CH₂), 5.69–5.79 (m, 1 H, CH=), 6.60 (s, 1 H, 8-H), 6.65 (s, 1 H, 5-H), 6.80 (br. s, 1 H, NH) ppm. ¹³C NMR (100.6 MHz, CDCl₃, 25 °C): $\delta = 35.4$ (C-4), 43.2 (CH₂), 55.5 (C-1), 55.9 (OCH₃), 56.0 (OCH₃), 108.6 (C-8), 110.4 (C-5), 119.9 (=CH₂), 123.3 (C-4a), 125.6 (C-8a), 132.7 (CH=), 147.9 (C-6), 148.5 (C-7), 171.2 (CO) ppm. HRMS: calcd. for C₁₄H₁₇NO₃ [M + H]⁺ 248.1288; found 248.1278.

(1S)-1-[2-(1,3-Dioxan-2-yl)ethyl]-6,7-dimethoxy-3-oxo-1,2,3,4-tetrahydroisoquinoline (6i): Operating as described in the general procedure, from **5i** (114 mg, 0.26 mmol) in THF (2 mL) and NH₃ (30 mL) a residue was obtained. Flash chromatography (9:1 EtOAc/EtOH) afforded **6i** (78.5 mg, 92%) as a white solid. $[\alpha]_D^{25} = +2.3$ ($c = 0.53$, CHCl₃). IR (KBr): $\tilde{\nu} = 1674, 3217$ cm⁻¹. ¹H NMR (400 MHz, CDCl₃, 25 °C): $\delta = 1.33$ (dm, $J = 13.2$ Hz, 2 H, 2'-H), 1.61–1.84 (m, 2 H, 1'-H), 1.87–1.94 (m, 1 H, CH₂CH₂O), 1.91–2.11 (m, 1 H, CH₂CH₂O), 3.56 (d, $J = 19.5$ Hz, 1 H, 4-H), 3.60 (d, $J = 19.5$ Hz, 1 H, 4-H), 3.74 (td, $J = 11.6, 0.8$ Hz, 2 H, CH₂CH₂O), 3.86 (s, 3 H, OCH₃), 3.87 (s, 3 H, OCH₃), 4.09 (ddd, $J = 11.6, 4.8, 1.2$ Hz, 2 H, CH₂CH₂O), 4.48–4.52 (br. m, 1 H, 1-H), 4.56 (t, $J = 4.8$ Hz, 1 H, CHO₂), 6.59 (s, 1 H, 8-H), 6.65 (s, 1 H, 5-H), 7.18 (s.a., 1 H, NH) ppm. ¹³C NMR (100.6 MHz, CDCl₃, 25 °C): $\delta = 25.7$ (CH₂CH₂O), 30.5 (C-1'), 33.0 (C-2'), 35.3 (C-4), 55.6 (C-1), 55.9 (OCH₃), 56.0 (OCH₃), 66.8 (CH₂O), 101.6 (CHO₂), 108.8 (C-8), 110.4 (C-5), 123.1 (C-4a), 126.6 (C-8a), 147.8 (C-6), 148.3 (C-7), 171.4 (CO) ppm. HRMS: calcd. for C₁₇H₂₃NO₅ [M + H]⁺ 322.1655; found 322.1650.

2-Benzyl-4,5-dimethoxyphenylacetamide (8): Operating as described in the general procedure, from **5c** (100 mg, 1.17 mmol) in THF (2 mL) and NH₃ (30 mL) a residue was obtained. Flash chromatography (EtOAc) afforded **8** (20 mg, 28%). IR (KBr): $\tilde{\nu} = 1629, 2933$ cm⁻¹. ¹H NMR (400 MHz, CDCl₃, 25 °C): $\delta = 3.44$ (s, 2 H, CH₂CO), 3.81 (s, 3 H, OCH₃), 3.85 (s, 3 H, OCH₃), 3.93 (s, 2 H, CH₂Ar), 5.20 (s, 1 H, NH₂), 5.90 (s, 1 H, NH₂), 6.70 (s, 1 H, 3-H), 6.75 (s, 1 H, 6-H), 7.10–7.25 (m, 5 H, ArH) ppm. ¹³C NMR (100.6 MHz, CDCl₃, 25 °C): $\delta = 38.8$ (CH₂Ar), 40.2 (CH₂CO), 55.9 (OCH₃), 56.0 (OCH₃), 113.8 (C-3), 114.2 (C-6), 125.5 (C-1), 126.3 (C-*p*), 128.5 (C-*m*), 128.6 (C-*o*), 131.6 (C-2), 140.3 (C-*i*), 147.8 (C-4), 148.3 (C-5), 173.9 (CO) ppm. HRMS: calcd. for C₁₇H₁₉NO₃ [M + H]⁺ 286.1443; found 286.1437.

General Procedure for the NaBH₄–I₂ Reduction Reactions: A solution of iodine (1 equiv.) in THF was slowly added to a cooled (0 °C) suspension of NaBH₄ (2.5 equiv.) in anhydrous THF, and the mix-

ture was stirred at this temperature for 30 min. Then, a solution of lactam **6** (1 equiv.) in THF was added to the solution (0 °C). The resulting mixture was heated at reflux for 16 h and cooled to 0 °C. MeOH (4 mL) was slowly added, and the stirring was continued at room temperature for 30 min. The solvent was evaporated, and the resulting solid was digested with 2 N NaOH (30 min). The resulting suspension was extracted with CH₂Cl₂, the combined organic extracts were dried and concentrated, and the residue was purified by chromatography.

(–)-Salsolidine (7a): Following the above general procedure, from lactam **6a** (100 mg, 0.45 mmol) in THF (5 mL), NaBH₄ (42.6 mg, 1.13 mmol) in THF (5 mL), and I₂ (114 mg, 0.45 mmol) in THF (4 mL), tetrahydroisoquinoline **7a** (65 mg, 70%) was obtained as an oil after flash chromatography (9:1 EtOAc/EtOH). $[α]_D^{25} = -58.5$ ($c = 0.50$, EtOH) {lit.^[1b] $[α]_D^{25} = -62.5$ ($c = 0.1$, EtOH)}. IR (KBr): $\tilde{\nu} = 3217\text{ cm}^{-1}$. ¹H NMR (300 MHz, CDCl₃, 25 °C): $\delta = 1.43$ (d, $J = 6.5$ Hz, 3 H, CH₃), 1.78 (br. s, 1 H, NH), 2.60–2.68 (dt, $J = 16.0$, 4.8 Hz, 1 H, 4-H), 2.74–2.84 (ddd, $J = 16.0$, 8.4, 5.4 Hz, 1 H, 4-H), 2.99 (ddd, $J = 13.0$, 8.4, 4.8 Hz, 1 H, 3-H), 3.24 (ddd, $J = 13.0$, 4.8 Hz, 1 H, 3-H), 3.87 (s, 6 H, 2 OCH₃), 4.04 (q, $J = 6.5$ Hz, 1 H, 1-H), 6.57 (s, 1 H, 8-H), 6.62 (s, 1 H, 5-H) ppm. ¹³C NMR (100.6 MHz, CDCl₃, 25 °C): $\delta = 22.8$ (CH₃), 29.5 (C-4), 41.8 (C-3), 51.2 (C-1), 55.8 (OCH₃), 55.9 (OCH₃), 109.0 (C-8), 111.7 (C-5), 126.8 (C-4a), 132.5 (C-8a), 147.2 (C-7), 147.3 (C-6) ppm.

(1S)-1-Ethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (7b): Following the above general procedure, from lactam **6b** (91 mg, 0.39 mmol) in THF (10 mL), NaBH₄ (36 mg, 1.1 mmol) in THF (4 mL), and I₂ (99 mg, 0.39 mmol) in THF (4 mL), tetrahydroisoquinoline **7b** (52 mg, 60%) was obtained as an oil after flash chromatography by using a cartridge containing amine-functionalized silica (7:3 hexane/EtOAc to EtOAc). $[α]_D^{25} = -47.4$ ($c = 0.3$, CH₂Cl₂) {ref.^[25] $[α]_D^{25} = -51.9$ ($c = 2.1$, CH₂Cl₂)}. IR (KBr): $\tilde{\nu} = 2930\text{ cm}^{-1}$. ¹H NMR (400 MHz, CDCl₃, 25 °C): $\delta = 1.02$ (t, $J = 7.6$ Hz, 3 H, CH₃), 1.67–1.78 (m, 1 H, CH₂), 1.90 (dddd, $J = 14.4$, 7.2, 7.2, 3.2 Hz, 1 H, CH₂), 2.40 (s, 1 H, NH), 2.67 (dt, $J = 16.2$, 5.2 Hz, 1 H, 3-H), 2.77 (dt, $J = 16.2$, 6.0 Hz, 1 H, 3-H), 2.98 (ddd, $J = 12.4$, 7.6, 4.8 Hz, 1 H, 4-H), 3.24 (dt, $J = 12.4$, 5.2 Hz, 1 H, 4-H), 3.85 (s, 6 H, 2 OCH₃), 3.85 (m, 1 H, 1-H), 6.57 (s, 1 H, 8-H), 6.62 (s, 1 H, 5-H) ppm. ¹³C NMR (100.6 MHz, CDCl₃, 25 °C): $\delta = 10.9$ (CH₃), 29.0 (CH₂), 29.4 (C-4), 41.1 (C-3), 55.8 (OCH₃), 56.0 (OCH₃), 56.7 (C-1), 109.2 (C-8), 111.7 (C-5), 127.1 (C-4a), 131.0 (C-8a), 147.2 (C-7), 147.3 (C-6) ppm. HRMS: calcd. for C₁₃H₁₉NO₂ [M + H]⁺ 222.1494; found 222.1488.

(–)-Norcryptostyline II (7d): Following the above general procedure, from lactam **6d** (90 mg, 0.26 mmol) in THF (3 mL), NaBH₄ (24.8 mg, 0.66 mmol) in THF (4 mL), and I₂ (66.5 mg, 0.26 mmol) in THF (3 mL), tetrahydroisoquinoline **7d** (58 mg, 69%) was obtained as a yellow oil after flash chromatography by using a cartridge containing amine-functionalized silica (1:1 hexane/EtOAc). $[α]_D^{25} = -33.8$ ($c = 0.36$, CHCl₃) {ref.^[5a] $[α]_D^{18} = -37$ ($c = 0.26$, CHCl₃)}. IR (KBr): $\tilde{\nu} = 2923\text{ cm}^{-1}$. ¹H NMR (400 MHz, CDCl₃, 25 °C): $\delta = 2.75$ (dt, $J = 15.2$, 4.4 Hz, 1 H, 4-H), 2.96 (ddd, $J = 15.2$, 4.8, 4.8 Hz, 1 H, 4-H), 3.06 (ddd, $J = 13.2$, 8.8, 4.8 Hz, 1 H, 3-H), 3.24 (ddd, $J = 13.2$, 4.8 Hz, 1 H, 3-H), 3.65 (s, 3 H, OCH₃), 3.83 (s, 3 H, OCH₃), 3.87 (s, 6 H, OCH₃), 5.00 (s, 1 H, 1-H), 6.27 (s, 1 H, 8-H), 6.62 (s, 1 H, 5-H), 6.79 (s, 1 H, 2'-H), 6.80 (s, 1 H, 6'-H), 6.82 (s, 1 H, 5'-H) ppm. ¹³C NMR (75.4 MHz, CDCl₃, 25 °C): $\delta = 29.1$ (C-4), 42.1 (C-3), 55.8 (OCH₃), 55.9 (OCH₃), 56.0 (OCH₃), 61.3 (C-1), 110.7 (C-2'), 110.9 (C-5'), 111.4 (C-8), 111.8 (C-5), 121.3 (C-6'), 127.4 (C-4a), 129.8 (C-8a), 136.9 (C-7), 147.0 (C-6), 147.7 (C-4'), 148.4 (C-7), 149.0 (C-3') ppm. HRMS: calcd. for C₁₉H₂₃NO₄ [M + H]⁺ 330.1705; found 330.1691.

(–)-Norcryptostyline III (7e): Following the above general procedure, from lactam **6e** (92 mg, 0.25 mmol) in THF (3 mL), NaBH₄ (23.3 mg, 0.62 mmol) in THF (4 mL), and I₂ (70.8 mg, 0.25 mmol) in THF (3 mL), tetrahydroisoquinoline **7e** (52 mg, 58%) was obtained as a yellow oil after flash chromatography by using a cartridge containing amine-functionalized silica (7:3 Et₂O/EtOAc). $[α]_D^{25} = -45.7$ ($c = 0.11$, CHCl₃) {ref.^[16a] $[α]_D = -37.0$ (CHCl₃)}. IR (KBr): $\tilde{\nu} = 2919\text{ cm}^{-1}$. ¹H NMR (300 MHz, CDCl₃, 25 °C): $\delta = 2.74$ (dt, $J = 15.6$, 4.5, 3.9 Hz, 1 H, 4-H), 2.90–3.00 (m, 1 H, 4-H), 3.07 (ddd, $J = 11.7$, 7.8, 3.9 Hz, 1 H, 3-H), 3.26 (dt, $J = 11.7$, 5.1, 4.5 Hz, 1 H, 3-H), 3.68 (s, 3 H, OCH₃), 3.81 (s, 6 H, 2 CH₃O), 3.85 (s, 3 H, OCH₃), 3.88 (s, 3 H, OCH₃), 5.01 (s, 1 H, 1-H), 6.26 (s, 1 H, 8-H), 6.47 (s, 2 H, 2'-H, 6'-H), 6.63 (s, 1 H, 5-H) ppm. ¹³C NMR (75.4 MHz, CDCl₃, 25 °C): $\delta = 27.9$ (C-4), 41.5 (C-3), 55.8 (OCH₃), 56.0 (OCH₃), 56.2 (OCH₃), 60.8 (OCH₃), 61.2 (C-1), 106.4 (C-2'), C-6'), 110.8 (C-8), 111.3 (C-5), 126.7 (C-4a), 129.8 (C-8a), 137.7 (C-1'), 147.4 (C-6), 148.2 (C-7), 153.2 (C-3', C-4', C-5') ppm. HRMS: calcd. for C₂₀H₂₅NO₅ [M + H]⁺ 360.1809; found 360.1809.

(–)-O,O-Dimethylcoclaurine (7f): Following the above general procedure, from lactam **6f** (200 mg, 0.6 mmol) in THF (3 mL), NaBH₄ (58 mg, 1.5 mmol) in THF (4 mL), and I₂ (152 mg, 0.8 mmol) in THF (3 mL), tetrahydroisoquinoline **7f** (111 mg, 59%) was obtained as a yellow oil after flash chromatography by using a cartridge containing amine-functionalized silica (8:2 to 1:1 hexane/EtOAc). $[α]_D^{25} = -11.8$ ($c = 0.5$, CHCl₃) {ref.^[18c] $[α]_D^{25} = -19.9$ ($c = 1$, CHCl₃)}. IR (KBr): $\tilde{\nu} = 2932\text{ cm}^{-1}$. ¹H NMR (400 MHz, CDCl₃, 25 °C): $\delta = 2.64$ –2.79 (m, 1 H, 3-H), 2.73 (ddd, $J = 11.6$, 6.0, 6.0 Hz, 1 H, 4-H), 2.86 (dd, $J = 14.0$, 9.5 Hz, 1 H, CH₂Ar), 2.91 (ddd, $J = 12.0$, 6.0, 5.6 Hz, 1 H, 3-H), 3.15 (dd, $J = 14.0$, 4.5 Hz, 1 H, CH₂Ar), 3.20 (ddd, $J = 11.6$, 11.6, 5.6 Hz, 1 H, 4-H), 3.80 (s, 1 H, OCH₃), 3.82 (s, 1 H, OCH₃), 3.86 (s, 1 H, OCH₃), 4.11 (dd, $J = 9.5$, 4.5 Hz, 1 H, 1-H), 6.59 (s, 1 H, 8-H), 6.63 (s, 1 H, 5-H), 6.86 (d, $J = 8.5$ Hz, 2 H, 3'-H), 7.16 (d, $J = 8.5$ Hz, 2 H, 5'-H) ppm. ¹³C NMR (100.6 MHz, CDCl₃, 25 °C): $\delta = 29.5$ (C-4), 40.7 (CH₂Ar), 41.5 (C-3), 55.3 (OCH₃), 55.8 (OCH₃), 55.9 (OCH₃), 56.9 (C-1), 109.4 (C-8), 111.8 (C-5), 114.0 (C-3'), 127.3 (C-4a), 130.3 (C-2'), 130.5 (C-1'), 131.0 (C-8a), 147.0 (C-7), 147.4 (C-6), 158.3 (C-4') ppm. HRMS: calcd. for C₁₉H₂₃NO₃ [M + H]⁺ 314.1756; found 314.1743.

(1S)-6,7-Dimethoxy-1-phenylethyl-1,2,3,4-tetrahydroisoquinoline (7g): Following the above general procedure, from lactam **6g** (250 mg, 0.8 mmol) in THF (3 mL), NaBH₄ (76 mg, 2.0 mmol) in THF (4 mL), and I₂ (203 mg, 0.8 mmol) in THF (3 mL), tetrahydroisoquinoline **7g** (183 mg, 77%) was obtained as a colorless oil after flash chromatography (SiO₂ previously washed with 8:2 Et₃N/EtOAc; 8:2 to 1:1 Et₂O/EtOAc as eluent). $[α]_D^{25} = -23.4$ ($c = 0.25$, CHCl₃). IR (KBr): $\tilde{\nu} = 2955\text{ cm}^{-1}$. ¹H NMR (400 MHz, CDCl₃, 25 °C): $\delta = 2.04$ –2.17 (m, 2 H, CH₂), 2.66–2.89 (m, 4 H, CH₂Ar, 4-H), 3.02 (ddd, $J = 12.0$, 7.2, 5.6 Hz, 1 H, 3-H), 3.27 (ddd, $J = 12.0$, 5.6, 5.6 Hz, 1 H, 3-H), 3.82 (s, 3 H, OCH₃), 3.85 (s, 3 H, OCH₃), 4.00 (dd, $J = 8.0$, 2.8 Hz, 1 H, 1-H), 6.57 (s, 2 H, 5-H, 8-H), 7.17–7.31 (m, 5 H, ArH) ppm. ¹³C NMR (75.4 MHz, CDCl₃, 25 °C): $\delta = 29.1$ (CH₂Ar), 32.4 (C-4), 38.1 (CH₂), 40.9 (C-3), 55.1 (C-1), 55.8 (OCH₃), 56.0 (OCH₃), 109.2 (C-8), 111.8 (C-5), 125.9 (C-4'), 127.0 (C-4a), 128.4 (C-2', C-3'), 128.5 (C-8a), 142.2 (C-4'), 147.3 (C-6), 147.4 (C-7) ppm. HRMS: calcd. for C₁₉H₂₃NO₂ [M + H]⁺ 298.1807; found 298.1802.

(1S)-1-[2-(1,3-Dioxan-2-yl)ethyl]-2-[(1R)-2-hydroxy-1-phenylethyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (9): LiAlH₄ (96 mg, 2.54 mmol) was slowly added to a suspension of AlCl₃ (113 mg, 0.85 mmol) in THF (6 mL) at –78 °C and the mixture was stirred for 2 h. Then, a solution of tetrahydroisoquinolone **5i** (170 mg,

0.39 mmol) in anhydrous THF (6 mL) was slowly added. The stirring was continued at -78°C for 20 h, and the reaction was quenched with water. The aqueous layer was extracted with CH_2Cl_2 , and the combined organic extracts were dried and concentrated to give a residue, which was purified by chromatography (Et_2O to 1:1 $\text{Et}_2\text{O}/\text{EtOAc}$) to afford tetrahydroisoquinoline **9** (144 mg, 87%). $[\alpha]_{\text{D}}^{25} = -37.1$ ($c = 1.03$, CHCl_3). IR (KBr): $\tilde{\nu} = 3399\text{ cm}^{-1}$. ^1H NMR (400 MHz, CDCl_3 , 25°C): $\delta = 1.26\text{--}1.31$ (m, 1 H, ClCH_2), $1.49\text{--}1.52$ (m, 1 H, OCH_2CH_2), $1.53\text{--}1.62$ (m, 1 H, CH_2CHO_2), $1.76\text{--}1.82$ (m, 1 H, CH_2CHO_2), $1.83\text{--}1.93$ (m, 1 H, OCH_2CH_2), $1.97\text{--}2.09$ (m, 1 H, ClCH_2), 2.27 (s, 1 H, OH), 2.43 (dd, $J = 17.0$, 5.0 Hz, 1 H, 4-H), 2.97 (ddd, $J = 17.0$, 12.0 , 6.0 Hz, 1 H, 4-H), 3.20 (dd, $J = 13.5$, 6.0 Hz, 1 H, 3-H), 3.31 (dd, $J = 13.5$, 5.0 Hz, 1 H, 3-H), 3.37 (dd, $J = 9.6$, 4.4 Hz, 1 H, 1-H), $3.64\text{--}3.67$ (m, 2 H, 2 OCH_2CH_2), $3.68\text{--}3.73$ (m, 1 H, CHAr), 3.75 (s, 3 H, OCH_3), 3.83 (s, 3 H, OCH_3), $3.81\text{--}3.86$ (m, 2 H, 2 OCH_2CH_2), 3.95 (dd, $J = 10.8$, 6.0 Hz, 1 H, CH_2OH), 4.05 (dd, $J = 10.8$, 4.8 Hz, 1 H, CH_2OH), 4.40 (t, $J = 4.8$ Hz, 1 H, CHO_2), 6.28 (s, 1 H, 8-H), 6.55 (s, 1 H, 5-H), $7.28\text{--}7.29$ (m, 5 H, ArH) ppm. ^{13}C NMR (75.4 MHz, CDCl_3 , 25°C): $\delta = 22.5$ ($\text{CH}_2\text{CH}_2\text{O}$), 25.6 (C-4), 30.7 (C-1'), 32.1 (C-2'), 39.0 (C-3), 55.6 (OCH_3), 55.7 (OCH_3), 57.6 (C-1), 64.0 (CH_2OH), 64.5 (CHAr), 66.6 (OCH_2CH_2), 102.1 (CHO_2), 110.5 (C-8), 111.3 (C-5), 125.4 (C-4a), 127.4 (C-p), 128.2 (C-o), 128.6 (C-m), 130.3 (C-8a), 140.9 (C-i), 146.9 (C-6), 147.1 (C-7) ppm. HRMS: calcd. for $\text{C}_{25}\text{H}_{33}\text{NO}_5$ $[\text{M} + \text{H}]^+$ 428.2437; found 428.2424.

(S)-(-)-Crispine A: A solution of tetrahydroisoquinoline **9** (110 mg, 0.26 mmol) in EtOH (12 mL) and 1.0 M aqueous HCl (0.5 mL) containing 10% Pd/C (15 mg) was hydrogenated with vigorous stirring at room temperature and atmospheric pressure for 3 d. The catalyst was removed by filtration, the solvent was concentrated under vacuum, and the resulting oil was purified by chromatography with a cartridge containing amine-functionalized silica (1:1 hexane/EtOAc) to give crispine A (45 mg, 74%). $[\alpha]_{\text{D}}^{25} = -100.1$ ($c = 0.32$, CHCl_3) {ref.^[26] $[\alpha]_{\text{D}}^{25} = -96$ ($c = 0.25$, CHCl_3)}. IR (KBr): $\tilde{\nu} = 2922\text{ cm}^{-1}$. ^1H NMR (400 MHz, CDCl_3 , 25°C): $\delta = 1.69\text{--}1.78$ (m, 1 H, 1-H), $1.82\text{--}1.99$ (m, 2 H, 2-H), $2.30\text{--}2.38$ (m, 1 H, 1-H), 2.63 (ddd, $J = 17.0$, 8.0 , 8.0 Hz, 1 H, 6-H), 2.69 (m, 1 H, 5-H), 2.74 (m, 1 H, 3-H), 3.00 (ddd, $J = 12.4$, 9.6 , 5.6 Hz, 1 H, 3-H), 3.07 (ddd, $J = 17.0$, 8.0 , 4.0 Hz, 1 H, 6-H), 3.18 (dddd, $J = 17.2$, 11.2 , 6.4 , 2.8 Hz, 1 H, 5-H), 3.49 (m, 1 H, 10b-H), 3.85 (s, 6 H, OCH_3), 6.57 (s, 1 H, 10-H), 6.61 (s, 1 H, 7-H) ppm. ^{13}C NMR (75.4 MHz, CDCl_3 , 25°C): $\delta = 22.3$ (C-2), 27.9 (C-6), 30.6 (C-3), 48.2 (C-3), 53.1 (C-5), 55.9 (OCH_3), 56.0 (OCH_3), 62.8 (C-10b), 108.8 (C-10), 111.3 (C-7), 126.1 (C-6a), 130.5 (C-10a), 147.3 (C-8), 147.4 (C-9) ppm. HRMS: calcd. for $\text{C}_{14}\text{H}_{19}\text{NO}_2$ $[\text{M} + \text{H}]^+$ 234.1494; found 234.1486.

Acknowledgments

Financial support from the Ministry of Science and Innovation, Spain (Project CTQ2009-07021/BQU) and the AGAUR, Generalitat de Catalunya (Grant 2009-SGR-111) is gratefully acknowledged.

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Received: April 7, 2010

Published Online: June 11, 2010